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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/02, 47/34, 47/36

A1

(11) International Publication Number: **WO 97/30693**

(43) International Publication Date: 28 August 1997 (28.08.97)

(21) International Application Number: PCT/KR97/00032

(22) International Filing Date: 25 February 1997 (25.02.97)

(30) Priority Data:
1996/4566 26 February 1996 (26.02.96) KR

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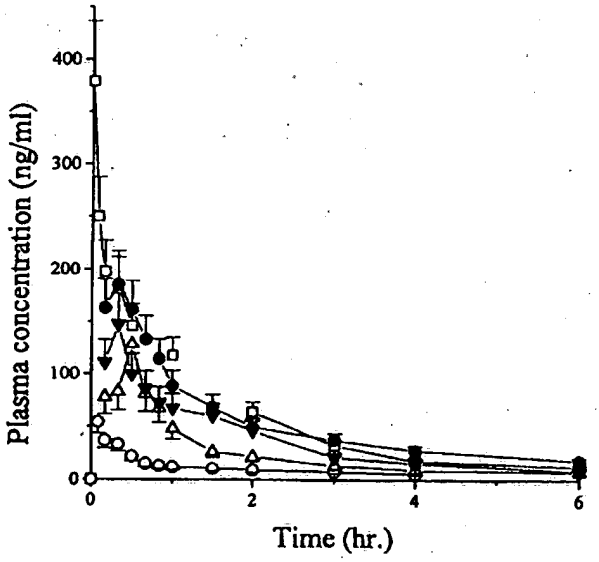
(81) Designated States: CA, CN, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUPPOSITORY COMPOSITION OF THE DRUG WHICH UNDERGO THE HEPATIC FIRST-PASS EFFECT

(57) Abstract

This invention relates to a suppository composition containing a drug which undergoes the hepatic first-pass effect, poloxamer and hydrophilic natural polymers. The suppository composition of this invention is characterized in that: has the gelation temperature of 30 to 36 °C, and is a liquid form at room temperature, and readily becomes a gel at body temperature after rectal administration; has the remarkable gel strength, and is not leaked out the anus; has the remarkable bioadhesive force, and doesn't climb up to the end of the colon, therefore ensures better bioavailability of the drug.



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THE TITLE OF INVENTION

Suppository composition of the drug
which undergo the hepatic first-pass effect

TECHNICAL FIELD

This invention relates to the suppository composition of the drug which undergo the hepatic first-pass effect and more particularly, a suppository composition of the drug which undergo the hepatic first-pass effect, being characterized in that said composition;

- has the gelation temperature of 30 to 36℃, and is a liquid form at room temperature, and readily becomes a gel at body temperature after rectal administration;
- has the remarkable gel strength, and is not leaked out from the anus;
- has the remarkable bioadhesive force, and doesn't climb upto the end of the colon, therefore ensures better bioavailability of the drug.

BACKGROUND ART

The oral drug administration is the commonest method designed to apply the drugs into the human body. However, some drugs are absorbed from the gastrointestinal tract and eliminated by the hepatic first-pass effect, thus giving lower bioavailability and significant reduction of therapeutic efficacy thereto. The drugs which undergo the hepatic first-pass effect include propranolol, alprenol, metoprolol, isoproterenol, oxprenolol, pindolol, testosterone, methyltestosterone, epinephrine, imipramine, desmethylimipramine, nortryptyline, oxyphenbutazone, tryptophan, serotonin, pheniprazine, morphine, lidocain, propoxyphene, salicylamide, hexobarbital, phenyltoin, quarternary ammonium salt, pentazocine, diltiazem, nifedipine, nitrandipine, and cyclosporin A. In an effort to enhance their bioavailability, these drugs in an injectable form are being given but it has recognized several disadvantages in that a)

administration is inconvenient, b) most of patients dislike an injection, and c) drug's direct infusion into the blood vessel is very dangerous.

In order to overcome these shortcomings as aforementioned, there have been several approaches to change the administration route of drugs which undergo the hepatic first-pass effect, into other alternative routes via nose, skin, rectum or etc. However, said administration routes cannot completely meet the desired objectives in that;

- Nasal administration of propranolol is deemed inconvenient for the handling and administration of dosage form(Hussain et al., *J. Pharm. Sci.*, 69, 1411-1413, 1980);
- The possible skin-permeation tests of drug using multilaminate adhesive device or iontophoresis show that the amount of drug permeated through skin is so small that the transdermal administration of drug cannot achieve the target dose(Corbo et al., *Pharm. Res.*, 6(9), 753-758, 1989; Singh et al., *J. Control. Rel.*, 18, 165-170, 1992);
- Rectal administration when dosage is given induces disgusting feeling and discomforts and after administration the dosage climbs upto the end of the colon by peristalsis, therefore the drug is absorbed there and undergo the hepatic first-pass effect. Thus said administration route has failed to get over the aforementioned defects completely.

In case of testosterone, there have been some approaches of the buccal and the transdermal administration but failed due to insufficient amount of drugs permeated through mouth mucosa and skin.

The inventor et al. have noticed the rectal administration of drugs which undergo the hepatic first-pass effect and in order to get over the aforementioned shortcomings associated with said rectal administration, poloxamer as suppository base is under careful consideration since such base is in a liquid phase at low temperature but when temperature goes up, it becomes in a gel phase.

In recent years, considerable interest has focused on some approaches to apply the poloxamer into the human body. For example the

U.S. Pat. No. 4,188,373 discloses the adjustment of gelation temperature depending on varied concentrations of poloxamer and the Canadian Pat. No. 1,072,413 also discloses varied gelatin temperatures of bases through mixing with Tetronic® and Tergitol®, poloxamer derivatives.

Several U.S. Pat. Nos. 4,478,822, 4,474,751, 4,474,752 and 4,474,753 also disclose that using poloxamer as a base, various kinds of additive are employed so as to adjust the ion strength and pH as well as to apply it into skin, eye and the body cavity such as rectum and urinary tract.

However, the conventional gel composition using said poloxamer has some disadvantages in that when rectal administration is given, due to undesirable conditions of gelation temperature, gel strength and bioadhesive force, the dosage may be leaked out from the anus, or climb upto the end of the colon. Thus the drug of that dosage form may not be absorbed, or that absorbed at colon undergo the hepatic first-pass metabolism.

The Europe Patent No. 0 551 626 A1 discloses that with pH adjustment and addition of carbomer, said poloxamer with increased gelation temperature and viscosity is applied to skin, eye, rectum and urinary tract. Nevertheless, this invention has proven insufficient in its application to the suppository composition since it does not consider the bioadhesive force and dissolution.

DISCLOSURE OF THE INVENTION

In order to overcome the aforementioned shortcomings, therefore, the inventor et al. have endeavored to develop a suppository composition of the drug which undergo the hepatic first-pass effect with better bioavailability.

An object of this invention is to provide a suppository composition of the drug which undergo the hepatic first-pass effect, being characterized in that;

- Any disgusting feeling or discomforts does not occur, when a drug is administered;
- Administration is easy and after administration a composition is not leaked out from the anus or does not climb upto the end of the colon, thus ensuring better bioavailability.

The suppository composition of this invention comprises 0.1～10 weight part of a drug which undergoes the hepatic first-pass effect, 25～40 weight part of poloxamer and 0.1～1 weight part of hydrophilic natural polymers to the total blending ratio.

The drug, contained in the composition of this invention, which undergo the hepatic first-effect, may be selected from the following materials: propranolol, alprenol, metoprolol, isoproterenol, oxprenolol, pindolol, testosterone, methyltestosterone, epinephrine, imipramine, desmethylimipramine, nortryptyline, oxyphenbutazone, tryptophan, serotonin, pheniprazine, morphine, lidocain, propoxyphene, salicylamide, hexobarbital, phenyltoin, quarternary ammonium salt, pentazocine, diltiazem, nifedipine, nitrandipine, cyclosporin A and etc.. In case of the amount of this drug, 0.1～10 weight part is contained to the total suppository composition; If less than 0.1 weight part is contained, relatively enlarged volume of said composition at single dose makes it difficult to perform the rectal administration but in case of exceeding 10 weight part, the drug itself reduces the gel strength and bioadhesive force so that the adjustment of that properties become difficult.

From the suppository composition of this invention, one or more poloxamers may be selected from the following, i.e., solid-phase type (F-127, F-108, F-98, F-88, F-68 and etc.), liquid-phase type (L-44, L-62, L-64 and etc.) and paste type (P-85, P-81, P-123 and etc.). It is preferred to contain 25～40 weight part of poloxamer to the suppository composition; if less than 25 weight part is contained, the gel strength and bioadhesive force are weak and in case of exceeding 40 weight part, higher degree of

viscosity makes it difficult to manufacture the desired product.

These poloxamers adjust the gelation temperature of the suppository composition to 30~36℃; thus, said poloxamers are in liquid phase at room temperature and in gel state within the body.

The hydrophilic natural polymers contained in the suppository composition of this invention may be used by selecting chitosan and sodium alginate independently or in a mixing form.

About 0.1~1 weight part of hydrophilic natural polymers is contained to the suppository composition; if less than 0.1 weight part is contained, the gel strength and bioadhesive force cannot be adjusted and sustained drug release is unavailable. Meantime, in case of exceeding 1 weight part, higher degree of viscosity makes it difficult to manufacture the desired product.

Since these hydrophilic natural polymers have hydrophilic groups such as amine group (NH_2) or hydroxyl group (OH) at the end of the molecular structure which may be reacted with hydroxyl group (OH) of poloxamer by hydrogen bond, more strong three-dimensional net-working structure of poloxamer may be formed. In addition to that, these polymers can form the strong hydrogen bond with oligosaccharide groups of rectal mucosa. Therefore, very small amount of those can play a role to reinforce the gel strength and bioadhesive force. Further these hydrophilic natural polymers release the drug slowly by their matrix formation at a constant concentration.

In addition to the drugs which undergo the hepatic first-pass effect, poloxamer and hydrophilic natural polymers, the suppository composition of this invention may also include the following additives which may be commonly applied to the conventional dosage form of rectal administration: preservatives (e.g., sodium benzoate, potassium sorbate, paraben derivatives and etc.), pH modulator (e.g., hydrochloric acid, citric acid, sodium hydroxide and etc.), stabilizers (e.g., methionine, etc.) and etc..

The suppository composition according to this invention may be prepared by dissolving these compositions in an appropriate amount of water.

The suppository composition of this invention is characterized in that;

- has the gelation temperature of 30 to 36 ℃, and is a liquid form at room temperature, and readily becomes a gel at body temperature after rectal administration;
- has the remarkable gel strength, and is not leaked out the anus;
- has the remarkable bioadhesive force, and doesn't climb upto the end of the colon, therefore ensures better bioavailability of the drug. Therefore, the suppository composition of this invention may improve a poor bioavailability that the conventional suppository composition faces, i.e., after rectal administration a composition climb upto the end of the colon by peristalsis of the large intestine, and the drug is absorbed there and undergo the hepatic first-pass effect.

With simple manufacturing process, the suppository composition may be easily manufactured with cost-saving effects.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the gelation temperature, when polymers are added.

Fig. 2 is a graph showing the gel strength, when polymers are added.

Fig. 3 is a graph showing the bioadhesive force, when polymers are added.

Fig. 4 is a graph showing the dissolution-controlling capacity, when polymers are added.

Fig. 5 is a graph showing the results of dissolution tests related to the suppository composition of Example 1 ~ 4.

Fig. 6 shows the plasma concentration of propranolol, when

suppository composition of Example 2, comparative suppository composition and conventional suppository compositions are administered via rectum and propranolol solution are administrated via injection and mouth, respectively.

BEST MODE FOR CARRING OUT THE INVENTION

This invention is explained in more detail by the following examples, but the claims are not limited to these examples.

EXAMPLE 1-4

The blending ratio involving the suppository composition according to Example 1-4 is shown in the following table 1. In the blending ratio as shown hereunder, poloxamer and hydrophilic natural polymers were dissolved in water and then, drugs and other components were successively added to the mixture for dissolving completely. Then, water was added to be a total of 100g in the weight of this mixture and the suppository composition was finally prepared.

Table 1. Blending ratio for the suppository composition according to Example 1-4

composition		example 1	example 2	example 3	example 4
poloxamer	F-127	15	15		20
	F-108			12	
	F-88			18	20
	F-68	19	15		
hydrophilic natural polymer	sodium alginate	02	06		
	chitosan			05	08
drug	propranolol	0.4	2.0		
	testoterone			0.1	
	epinephrine				8.0
additives	methyl parahydroxybenzoate	0.06		0.06	
	propyl parahydroxybenzoate	0.03		0.03	
	sodium benzoate				0.1
	citric acid				0.01
water		appropriate	appropriate	appropriate	appropriate
total (g)		100.0	100.0	100.0	100.0

COMPARATIVE EXAMPLE 1-4

In the same manner as described in the above compositions of Example 1-4, each composition without addition of hydrophilic natural polymers was prepared.

EXPERIMENTAL EXAMPLE 1: Selection of polymers adaptable to a suppository composition

For the selection of some polymers adaptable to suppository composition of propranolol, each of the following materials by 1 weight part such as polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), carbopol, polycarbophil, sodium alginate and chitosan was added to the mixing solution of poloxamer [F-127/F-68(15/15 weight part)], thus manufacturing the suppository compositions. The gelation temperature, gel strength and bioadhesive force related to each composition were measured. Further 2 weight part of each propranolol were added to the suppository composition, so prepared, so as to measure the dissolution rate of propranolol.

The testing criteria on the gelation temperature, gel strength, bioadhesive force and dissolution rate were as follows:

Gelation temperature: 10g of sample of the suppository composition was charged to a 20ml container, together with magnetic bar and installed to water bath at 4℃. With a digital thermometer inserted into the sample so as not to contact with the magnetic bar, the sample was stirred at a constant rate and while increasing its temperature at a rate of 1℃/min, the gelation temperature was determined when the magnetic bar was completely stopped.

Gel strength: 50g of the suppository composition was charged to a 100ml-mass cylinder and equilibrated in water bath at 36.5℃ for 30 mins. With a gel strength device placed on a mass cylinder, the gel strength was determined by time (second) when the device went down to 5cm.

Bioadhesive force: Two sections of tissue cut from the rectal mucosa of rabbit were attached to two vials of a bioadhesive force device and between them, 0.05g of the suppository composition was added. Then, with counterpoises piled up successively, the counterpoise weight

when said vials fall was calculated as a force extended per unit area.

Dissolution rate: 1g of the suppository composition was charged to a semi-permeable membrane and with both sides fastened with threads, the dissolution test was performed in phosphate buffer solution of pH 6.8 at 100 rpm using the paddle method. The small amount of medium was sampled at one hour intervals for analysis thereof.

These results are shown in the following table 1 and Fig. 1-4.

Fig. 1 is a graph showing the effect of the kinds of polymers on the gelation temperature. The gelation temperature of suppository composition was somewhat affected by the polymers irrespective of their kinds.

Fig. 2 is a graph showing the effect of the kinds of polymers on the gel strength and Fig. 3 is a graph showing the effect of the kinds of polymers on the bioadhesive force.

Compared with the suppository composition containing polyvinylpyrrolidone, hydroxypropylmethylcellulose, hydroxypropyl cellulose, carbopol or polycarbophil, the sodium alginate- or chitosan-containing suppository composition showed remarkably high gel strength and bioadhesive force.

Fig. 4 is a graph comparing the dissolution rate of propranolol from the suppository composition containing a certain scope of 0.2～0.8% concentration of sodium alginate and polycarbophil, respectively as hydrophilic polymers. While the suppository composition containing 0.2% sodium alginate showed higher dissolution rate than the polycarbophil-containing composition in same concentration, the composition containing 0.8% sodium alginate showed lower dissolution rate than the polycarbophil-containing composition in same concentration. This revealed that the composition containing a certain scope of 0.2～0.8% of sodium alginate as polymers had a wider range of propranolol dissolution than polycarbophil-containing composition, thus showing superior dissolution-controlling capacity of the former as a hydrophilic

polymer.

In the same manner as described in the above, some tests ascertained that carbopol-containing composition has similar dissolution range of polycarbophil-containing composition and chitosan-containing composition has similar dissolution range of sodium alginate-containing composition.

Since it was judged that sodium alginate and chitosan is superior to other polymers in terms of the gel strength, bioadhesive force and dissolution-controlling capacity. Therefore, the inventor et al. have selected sodium alginate and chitosan as polymers adoptable to the suppository composition of this invention.

EXPERIMENTAL EXAMPLE 2 : Measurement of gelation temperature, gel strength, leakage of the composition from the anus

The gelation temperature, gel strength and bioadhesive force of Comparative example 1-4 and Example 1-4 were measured in a same method as described in Experimental example 1. The animal experiments (assessment on leakage of the composition from the anus) were performed as follows:

- 1g of the suppository composition was inserted into the anus of rabbits in 5cm depth using a stomach sonde needle for rat and with rabbits placed at 45° slope obliquely, observations for 30 mins were made and the judgment was acceptable, when the drug suppository composition was not leaked out from the anus. Its results were shown in the following table 2.

Table 2. Measurement of gelation temperature, gel strength, leakage of the composition from the anus and bioadhesive force related to compositions of Comparative example 1-4 and of Example 1-4

experimental group	gelation temperature (℃)	gel strength (sec)	bioadhesive force (dyne/cm^2 $\times 10^2$)	leakage of the composition from the anus
example 1	33.4	16.0	108.0	No
comparative example 1	35.0	8.3	25.7	Yes
example 2	32.2	51.7	152.3	No
comparative example2	36.9	8.6	12.3	Yes
example 3	31.0	32.4	158.7	No
comparative example 3	34.7	4.3	15.6	Yes
example 4	33.1	19.2	62.6	No
comparative example 4	36.3	9.5	14.4	Yes

The above results showed that the suppository composition of Example 1-4 had lower gelation temperature, better gel strength/bioadhesive force and less leakage of the composition from the anus, than the composition of comparative example 1-4 without hydrophilic natural polymers

EXPERIMENTAL EXAMPLE 3: Dissolution test

Each dissolution rate related to 2g of the suppository composition of Example 1-2 and 1g of the suppository composition of Example 3-4 was measured in a same manner as described in Experimental example 1.

The experimental results were shown in Fig. 5 and the suppository composition of Example 1-4 has proven sufficient as a preparation.

EXPERIMENTAL EXAMPLE 4: Damage test of mucosal membrane

In order to assess each damage of the mucosal membrane induced by the suppository composition of Example 2, poloxamer, PEG 4000, Witepsol, comparative suppository composition [F-127/F-68/propranolol(15/15/2 weight part)], conventional suppository composition I [PEG 4000/propranolol (98/2 weight part)] and conventional suppository composition II [Witepsol/propranolol (98/2 weight part)], each group of 3 Sprague-Dawley rats, being fasted for 24-36 hours, was used for the following experiment.

Each suppository composition (0.1g) was inserted into the anus of rat in 5cm depth using a stomach sonde needle for rat. After 4 hrs, the rectum was harvested, cut by a knife and cleansed with physiological saline solution. The rectum was fixed with formaldehyde solution neutralized with 10% carbonate, followed by paraffin and stained with hematoxylin-eosin for microscopical observation.

The damage degree of the rectal mucosa was measured by the method of Reid et al. (Reid, A.S., et al., *Int. J. Pharm.*, 40, 181-185 (1987)), in which the following standards were applied:

Normal: The epithelium at interglandular site was normal.

Type I : Part of epithelium at interglandular site was torn apart or is tearing down.

Type II : The height of epithelium becomes generally low.

Type III : The epitheliums were completely torn apart, exposing the mucosae.

As the type passed into I, II and III, they showed the damage severity of the rectal mucosa. The value was calculated by percent (%). Its results were shown in table 3.

Table 3. Damage rate of rectal mucosa per type (Unit: %)

experimental group	normal	type I	type II	type III	total
normal mucosa	85.7±4.7	4.2±2.9	8.0±3.1	2.1±1.3	100
PEG 4000	60.4±4.5	7.0±2.7	20.6±7.8	12.0±3.3	100
Witepsol	16.0±6.6	8.0±2.6	20.4±4.6	55.6±12.3	100
F-127/F-68 (15/15%)	79.4±7.8	4.0±2.4	9.9±4.0	6.7±3.2	100
conventional suppository composition I	67.6±9.0	8.9±4.4	18.5±5.8	5.0±4.6	100
conventional suppository composition II	9.2±5.6	7.7±5.1	26.3±5.2	56.8±6.6	100
comparative suppository composition	44.9±9.1	7.2±2.6	27.6±8.1	20.3±11.6	100
example 2	72.3±7.7	5.0±1.6	15.9±7.9	6.8±4.9	100

From the above results, poloxamer as bases of the suppository composition of this invention showed more significant reduction in the damage rates of rectal mucosa than PEG 4000 and Witepsol as bases of conventional suppository and the suppository composition showed also less damage rates of rectal mucosa than conventional suppository compositions.

EXPERIMENTAL EXAMPLE 5: Location of composition after rectal administration

After rectal administration of the suppository composition of Example 2, comparative suppository composition and conventional suppository composition I, each location was measured as follows:

Each suppository composition(0.2g) containing 0.1% Blue No. 1 Lake coloring agent was inserted into the anus of rat in 5cm depth using a stomach sonde needle for rat. The rectums of rats were harvested at intervals of 5 min, 2 hrs and 4 hrs so as to ascertain the location of the

suppository composition. Its results were shown in the following table 4.

Table 4. Location of each composition after rectal administration

experimental group	5 min	2 hrs	4 hrs
conventional suppository composition I	4-5 cm	4-5 cm	7-8 cm
comparative suppository composition	4-5 cm	7-8 cm	7-8 cm
example 2	4-5 cm	4-5 cm	4-5 cm

The suppository composition of Example 2 was found at the place 4~5cm away from the anus even after 4 hrs, thus reflecting that said composition did not climb upto the large intestine, while the comparative suppository composition and conventional suppository composition I were found at the place 7~8cm away from the anus at the intervals of 2 hrs and 4 hrs, respectively, thus showing that said composition did not climb upto the large intestine.

EXPERIMENTAL EXAMPLE 6: Pharmacokinetics in suppository composition

Male rabbits, fasted for 24-36 hours, were used as experimental animals. In order to investigate the pharmacokinetics, the experimental animals were divided into the following 5 groups with each group containing 4 rabbits: i) intravenous injection group of propranolol solution(propranolol 20mg/water for injection 20ml), ii) oral administration group of propranolol solution(propranolol 20mg/water 20ml), iii) rectal administration group of conventional suppository composition I, iv) rectal administration group of the comparative suppository composition, and v) rectal administration group of the suppository composition of Example 2.

Rats were anesthetized with urethane and fixed them on a fixing stand. Then polyethylene tube was inserted into the right femoral artery and the suppository composition with a dose of propranolol 2mg/kg was given intravenously, orally or rectally. 0.5ml of blood sample from the right femoral artery was collected at certain intervals, centrifuged at 3000 rpm for 30 mins and harvested 0.2ml of plasma. 0.2ml of internal standard-acetonitrile(200mcg/ml) was added to the plasma and centrifuged at 3000 rpm for 10 mins to precipitate protein. The resulting solution was analyzed by HPLC. Its results were shown in table 5 and Fig. 6.

Table 5. AUC, T_{max}, C_{max}, K_{el} and $t_{1/2}$ on suppository composition

	AUC (hr·ng/ml)	MRT (hr)	T_{max} (min.)	C_{max} (ng/ml)	K_{el} (hr^{-1})	$t_{1/2}$ (hr)
intravenous injection of propranolol solution	363.91 ±61.21	1.91 ±0.34	-	-	0.46 ±0.07	1.50 ±0.22
oral administration of propranolol solution	48.92 ±7.31	3.10 ±0.42	7.00 ±2.45	54.44 ±16.30	0.24 ±0.09	2.93 ±0.62
rectal administration of conventional suppository compostion I	151.18 ±37.68	2.67 ±0.35	30.00 ±8.94	128.12 ±34.59	0.29 ±0.09	2.37 ±0.47
rectal administration of comparative suppository compostion I	225.78 ±30.67	2.27 ±0.34	22.50 ±4.33	147.10 ±50.01	0.43 ±0.08	1.63 ±0.31
rectal administration of example 2	318.33 ±42.34	3.19 ±0.48	26.00 ±4.90	185.82 ±52.17	0.27 ±0.08	2.55 ±0.53

From the above results, it was revealed that the bioavailability on the suppository composition of Example 2 was significantly higher than that of comparative suppository composition and conventional

suppository composition, while having similar level of bioavailability when injected intravenously.

CLAIMS

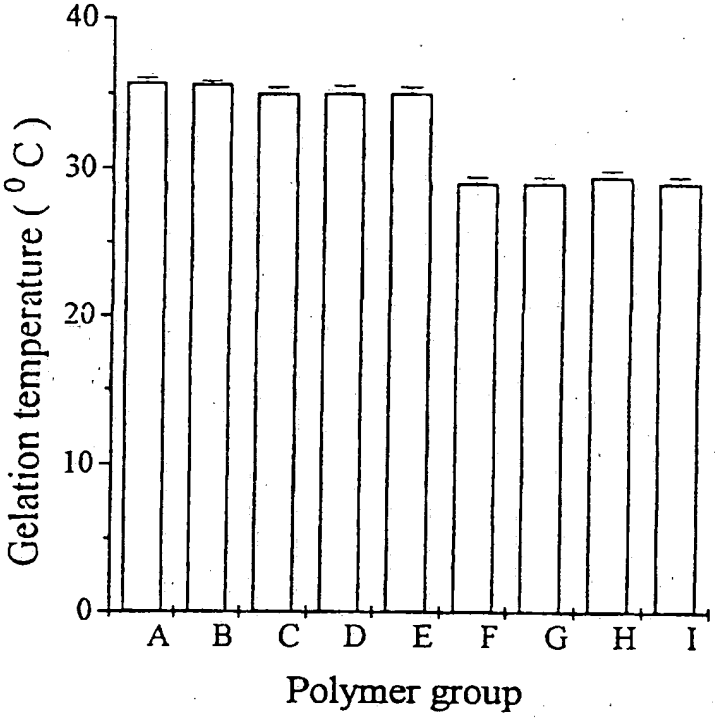
1. Suppository composition containing 0.1-10 weight part of a drug which undergoes the hepatic first-pass effect, 25-40 weight part of poloxamer and 0.1-1 weight part of hydrophilic natural polymers.

2. Suppository composition according to claim 1 wherein a drug which undergoes the hepatic first-pass effect is propranolol.

3. Suppository composition according to claim 1 wherein one or more poloxamers is/are selected from solid type, liquid type and paste type.

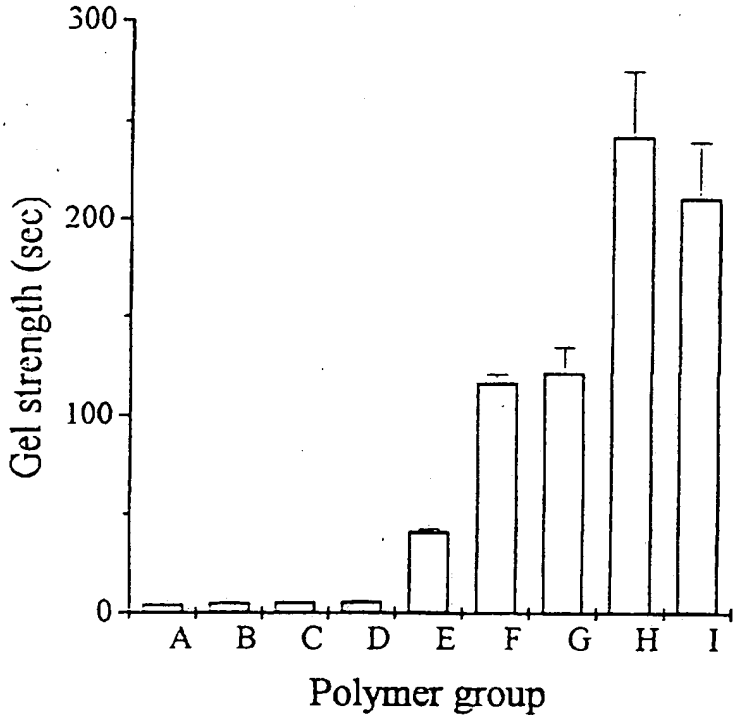
4. Suppository composition for rectal administration according to claim 1 wherein hydrophilic natural polymers are used from chitosan and sodium alginate independently or in a mixing form.

Fig. 1



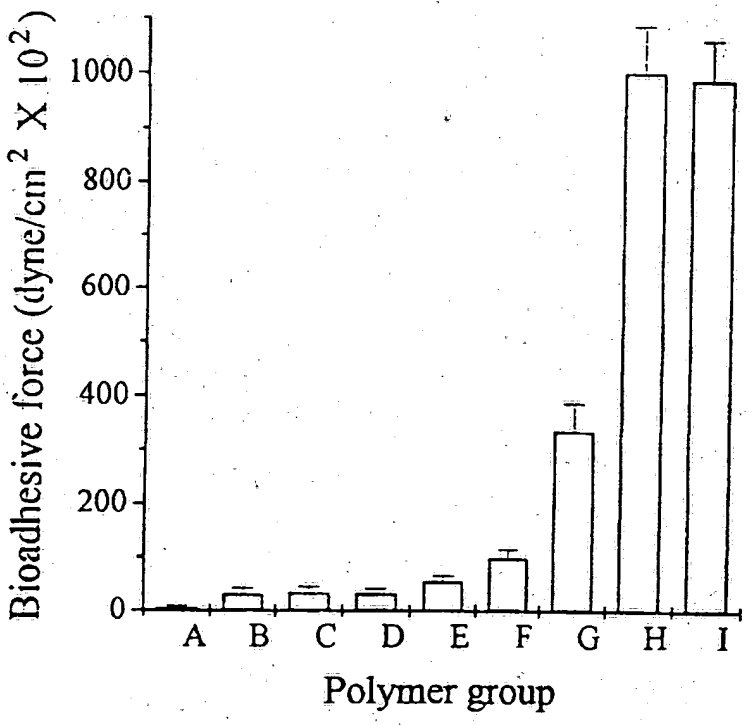
(A) F-127/F-68 (15/15 weight part)
(B) F-127/F-68/PVP (15/15/1 weight part)
(C) F-127/F-68/HPMC (15/15/1 weight part)
(D) F-127/F-68/HPC (15/15/1 weight part)
(E) F-127/F-68/sodium CMC (15/15/1 weight part)
(F) F-127/F-68/carbopol (15/15/1 weight part)
(G) F-127/F-68/polycarbophil (15/15/1 weight part)
(H) F-127/F-68/sodium alginate (15/15/1 weight part)
(I) F-127/F-68/chitosan (15/15/1 weight part)

Fig. 2



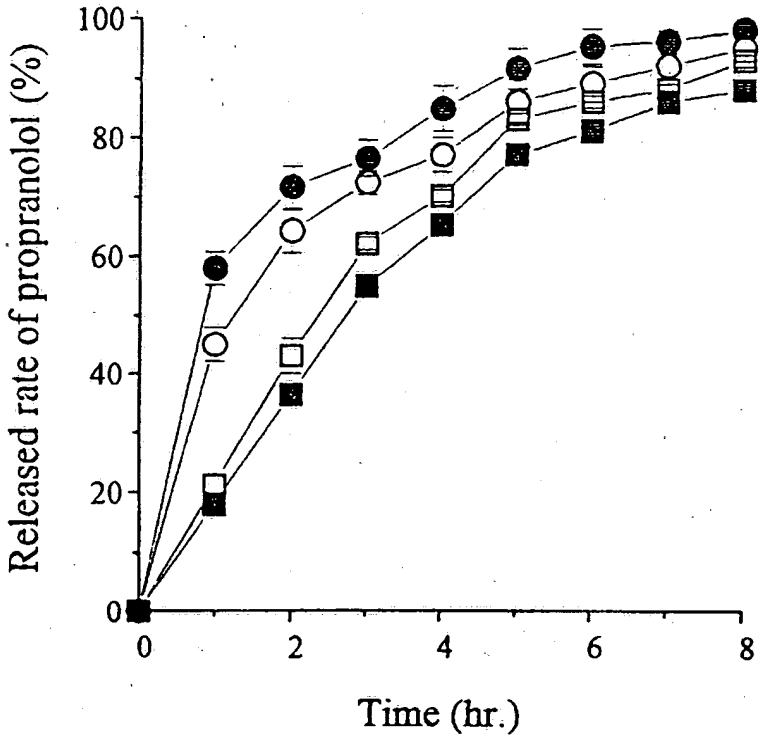
(A) F-127/F-68 (15/15 weight part)
(B) F-127/F-68/PVP (15/15/1 weight part)
(C) F-127/F-68/HPMC (15/15/1 weight part)
(D) F-127/F-68/HPC (15/15/1 weight part)
(E) F-127/F-68/sodium CMC (15/15/1 weight part)
(F) F-127/F-68/carbopol (15/15/1 weight part)
(G) F-127/F-68/polycarbophil (15/15/1 weight part)
(H) F-127/F-68/sodium alginate (15/15/1 weight part)
(I) F-127/F-68/chitosan (15/15/1 weight part)

Fig. 3



(A) F-127/F-68 (15/15 weight part)
(B) F-127/F-68/PVP (15/15/1 weight part)
(C) F-127/F-68/HPMC (15/15/1 weight part)
(D) F-127/F-68/HPC (15/15/1 weight part)
(E) F-127/F-68/sodium CMC (15/15/1 weight part)
(F) F-127/F-68/carbopol (15/15/1 weight part%)
(G) F-127/F-68/polycarbophil (15/15/1 weight part)
(H) F-127/F-68/sodium alginate (15/15/1 weight part)
(I) F-127/F-68/chitosan (15/15/1 weight part)

Fig. 4



-●- F-127/F-68/propranolol/sodium alginate (15/15/2/0.2 weight part)
-■- F-127/F-68/propranolol/sodium alginate (15/15/2/0.8 weight part)
-○- F-127/F-68/propranolol/polycarbophil (15/15/2/0.2 weight part)
-□- F-127/F-68/propranolol/polycarbophil (15/15/2/0.8 weight part)

Fig. 5

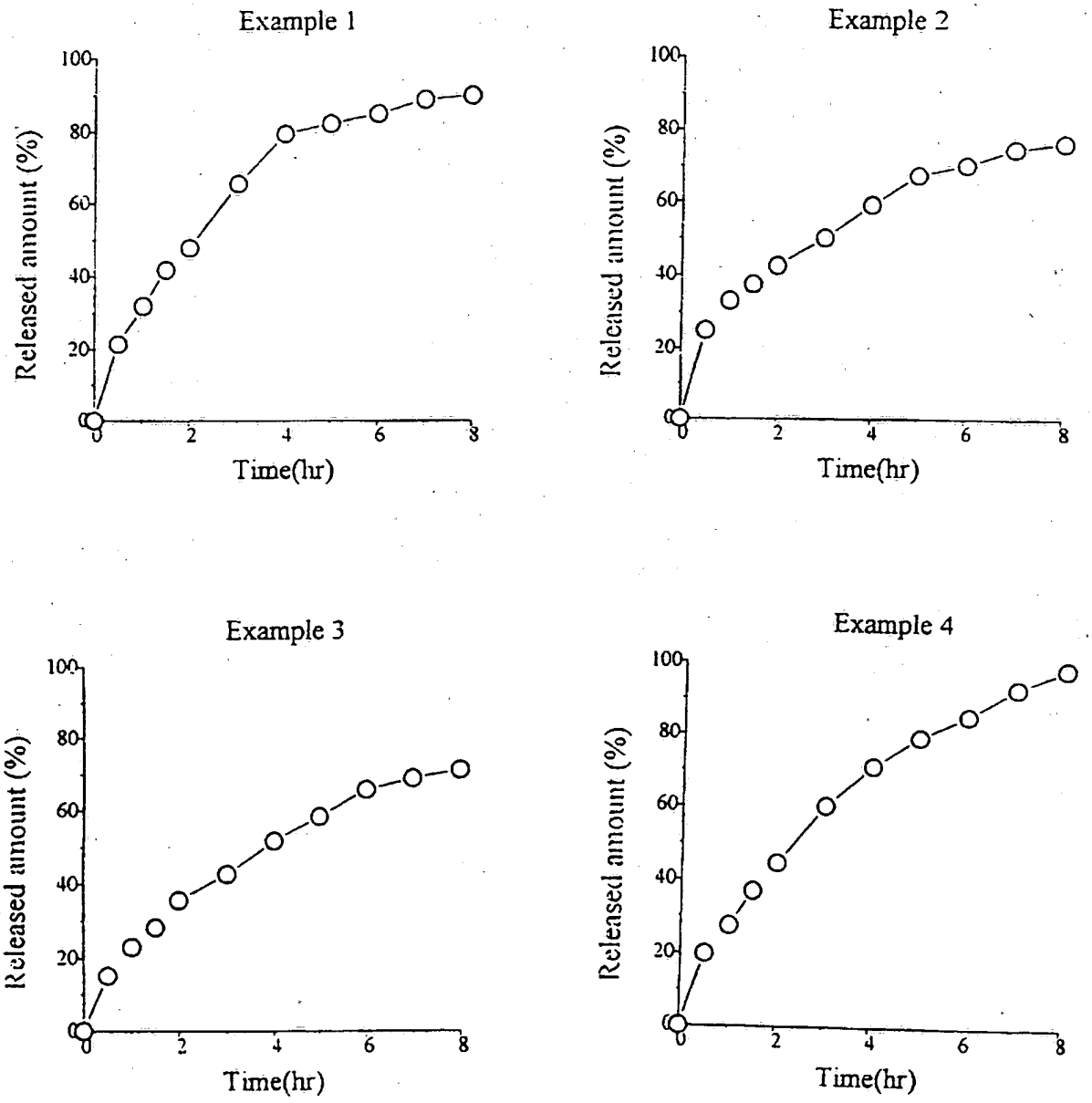
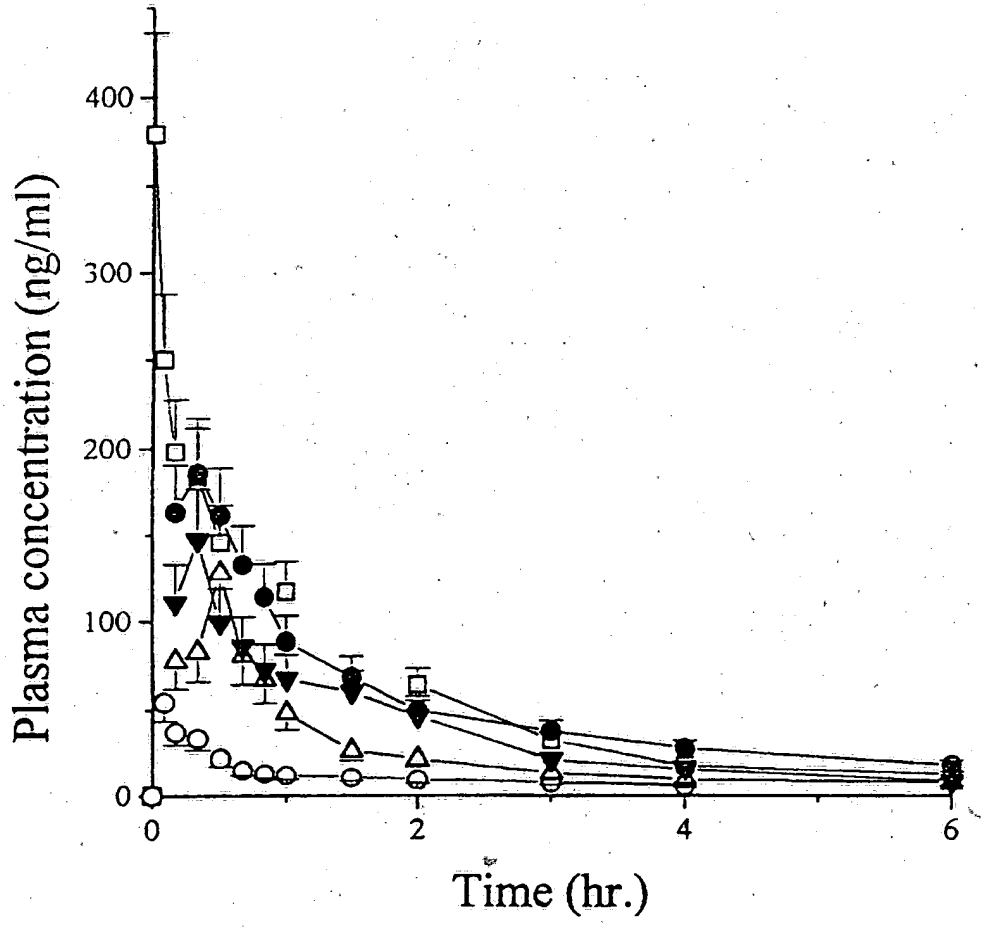

Example 1
Released amount (%)
Time(hr)
Example 2
Released amount (%)
Time(hr)
Example 3
Released amount (%)
Time(hr)
Example 4
Released amount (%)
Time(hr)

Fig. 6



-□- intravenous injection group of propranolol solution

-○- oral administration group of propranolol solution

-△- rectal administration group of conventional suppository composition I

-▼- rectal administration group of the comparative suppository composition

-●- rectal administration group of the suppository composition of Example 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00032

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: A 61 K 9/02, 47/34, 47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: A 61 K 9/02, 47/34, 47/36

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

QUESTEL-WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X Y	US 5 292 516 A (VIEGAS T.X. et al.) 08 March 1994 (08.03.94), claims 1-4; column 8, line 55 - column 9, line 24; abstract; column 6, line 52 - column 7, line 68; example 3.	1-3 4
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1997 (22.04.97)	13 May 1997 (13.05.97)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Mazzucco Telephone No. 1/5337058/33

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00032

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No.
PCT/KR 97/00032

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International application No.
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